Institution-based discovery: Immunochemistry, serological genetics and embryology at the California Institute of Technology

By Rebecca Mertens

PhD student, Department of Philosophy at Bielefeld University

Rebecca.mertens@uni-bielefeld.de

Introduction

The relationship between the California Institute of Technology (CalTech) and the Rockefeller Foundation (RF) in the mid-20th century is a famous example for the interplay between different kinds of science administration and their influence on the development of scientific programs. It has been illustrated several times that the RF had a huge impact on CalTech's scientific profile by means of general grant policies and the interactions between administrators and scientists.[i] Especially the collaboration between Linus Pauling, a trained structural chemist, and Warren Weaver, the director of the RF's Natural Science Division from 1932 to 1951, played a central role in this success story from the 1930s to the 1950s.[ii] In what follows, I will concentrate on the protein program that Weaver and Pauling started to develop in 1937 and that reached its peak in the 1940s and 50s. As many RF funded projects, this program was shaped by an ideal picture of basic science as cooperative and socially relevant enterprise, entertained and preserved through funding proposals and reports as well as through inner-institutional public-relation campaigns and journals.[iii] Conceptualized as a joint program between the Biology and Chemistry Division, the protein

program had a strong impact on other biochemical projects at the institute. This becomes visible most strikingly in the development of projects on immunology, embryology and serological genetics which, according to Lilly Kay, completely changed directions on the proposal level after their encounter with Pauling and his program on macromolecules.[iv] When I came to the Rockefeller Archive Center, I was mostly interested in the question of how this influence affected the transfer of ideas, hypotheses and heuristic strategies of embryologists and serological geneticists at CalTech.

The physico-chemical study of biological specificities

At the very beginning of his administration period as officer of RF's Natural Science Division, Weaver proposed a funding agenda that included a systematic plan of how to construct a long lasting influence America's scientific profile. In order to meet this goal, Weaver suggested to provide large funds for a few selected fields. As for the decisive funding criteria, Weaver wrote that

> "[i]t is proposed for the future program that interest in the fields in question be the dominant role in the selection process. […] The choice of fields of interest is influenced by several considerations. The field must contribute in a basic and important way of mankind; it must be sufficiently developed to merit support, but so imperfectly developed as to need it; it should be a field in which the contributions of the Foundation will play a critical role in producing and stimulating development that otherwise would not occur within reasonable time."[v]

Pauling's proposed project "on the structure of hemoglobin and related substances" (1934) seemed to have met exactly these conditions, as it held "large and immediate promise for application to basic problems in experimental biology."[vi] Weaver, who was excited by Pauling's outstanding reputation in physical chemistry, encouraged him to stick to problems with medical significance, and did everything he could to generously support his plans on chemical studies of fundamental problems in biology and medicine.[vii] In 1937,

Pauling's research at CalTech expanded into a program on the chemical features of macromolecules and related substance. The major goal of this program was a physico-chemical understanding of biological specificity. Chemists, biologists and physicists had very different conceptions of how specificity was to be characterized, and even within the respective disciplines specificity remained a loosely characterized concept.[viii] In his 1948 article on "The nature and forces between large molecules of biological interest", Pauling describes different kinds of specificities of large molecules, such as hemoglobin, enzymes and antibodies, and raises the assumption that

> "the same mechanism, dependent on a detailed complementariness in molecular structure, is responsible for all biological specificity. I think that enzymes are molecules that are complimentary in structure to the activated complexes of the reactions that they catalyze, that is, to the molecular configuration that is intermediate between the reacting substances and the products of reaction for these catalyzed processes. […] I believe that it is molecular size and shape, on the atomic scale, that are of primary importance in these phenomena […]."[ix]

Attempts to study the geometry of organic molecules started in the middle of the 19th century, most famously with Louis Pasteur's studies on tartaric acid and Jacobus Henricus van't Hoff's work on the asymmetric carbon atom.[x] Van't Hoff contributed to the already existent stereochemical movement by proposing a concrete model for the arrangement of atoms in a three-dimensional space. Other than Pasteur and his student Joseph-Achille Le Bel, van't Hoff proposed a molecular picture in which all atoms were arranged within a tetrahedra, with the carbon atom at the center.[xi] Up to the 1890s, conceptions of molecular geometry were mainly perceived as theoretical constructs. The study of sugars, their classification and synthesis, was one of the fields that contributed to the empirical accessibility of molecular geometry in the end of the 19th century. Especially Emil

Fischer's work on sugars and their fermentability was perceived as revolutionary in this respect and became known as one of the first programs that explicitly linked molecular geometry and biological function.[xii]

CalTech's protein researchers borrowed the conception of molecular geometry from late 19th century stereochemistry, but reinterpreted it with respect to physical principles and empirical results from X-ray analysis.[xiii] In one of the later reports of the Chemistry Division from 1951, the X-ray approach is described as an attack "from beneath – by determining the structure of amino acids, simple peptides and other simple substances closely related to proteins."[xiv] Pauling and his colleagues pointed out several times in proposals to the RF that such an approach was only doable within a rather open-ended research program and with long-term financial support.[xv] The hypothesis that molecular shape was the distinctive feature of important biological reactions legitimated the (expensive) X-ray diffraction methods for an audience that was interested in biological and medical issues.

Complementary reactions and institutional politics: Immunochemistry, serological genetics and embryology at CalTech

Pauling's work in immunology was deeply entangled with the larger program on the illumination of the chemical and physical features of proteins. Apart from the fact that antibodies were known to be proteins, the linkage between these two research fields was established by the assumption that two chemical agents must have complementary shapes in order to bring about a reaction of biological importance. The idea that all kinds of biological specificities (such as serological specificity, gene specificity and immunological specificity) could be understood as "antibody-antigen-like" or "enzyme-substrate-like" chemical reactions became a key element in CalTech's biochemical proposals and reports to the Rockefeller Foundation in the 1940s. Thus, at the

proposal level, the enzyme-substrate and the antibody-antigen framework served as a model for chemical complementarity and its causal power in biological processes. This can be shown by project descriptions of the group on embryology and serological genetics which seemed to be built entirely out of the enzyme-substrate and the antibody-gene analogy. In the 1946 biochemistry report to the RF this work is introduced and characterized as follows:

> "Most biological processes involve reactions in which the components exhibit remarkable specificity, the best known being the antigen-antibody and enzyme-substrate interaction. These fundamental problems of genetics and embryology which are characteristic by analogous specificities make up the field of our program in serological genetics and embryology. […] On the basis of investigations carried out during the last six years there is every indication of fruitful progress from this approach. It is now possible to foresee many specific routes along which these investigations should be pushed. The lines of future development must depend not only on the findings in this immediate field, but also in such related fields as physiological genetics, immunochemistry, enzyme chemistry and bio-synthesis of proteins, etc." [xvi]

Clearly, Pauling's reputation at the institute and the impact of his and Karl Landsteiner's 1940 published theory of antibody formation on the field of immunology played a role in the group's explicit orientation towards 'analogous specificities'.[xvii] The interest in the chemical study of phenomena of specificity and the relation between fields like immunology, serology and embryology, which seemed to be dealing with similar kinds of specificities, was, however, nourished long before Pauling entered the field, e.g. by the work of Landsteiner and Frank Rattray Lillie.[xviii] Nonetheless, efforts to combine these studies under the umbrella of a chemical specificity program at CalTech were not made before 1942. There is evidence that this cooperation was motivated by the active role of RF officers and mainly for administrative

reasons. In December 1942, Frank Blair Hanson, the RF Natural Science Division's associate director at that time, suggested a closer cooperation between the different groups working on problems related to immunology and indicated that the RF would eventually consider a well "thought through" larger program that combines the different interests.

> "We are in the somewhat unusual position at present of having two grants for the support of immunology at the California Institute of Technology. It would not be advisable for us to consider a third and independent grant in the same field, in the same institution. Dr. Sturtevant's grant expires next June, as does also the special one year-grant for immunological studies under Prof. Pauling. While I am not able to give any indication, at present, as to whether further support in this field is possible, it is nevertheless true that the officers would be willing to give serious consideration to a well thought through program in immunology involving the various interests in this field at Cal Tech. I would, therefore, suggest that you use this letter as the basis for further discussion with Professors Sturtevant and Pauling."[xix]

Hanson's advice was successful. In 1943, Tyler started to cooperate more closely with Alfred Sturtevant and Sterling Emerson on problems in immunology, embryology and serological genetics.[xx] In a recommendation letter to Hanson, George Beadle, who was at Stanford at that time, described Emerson's part of the project as investigating in the theory that the relation "between gene and antigen-antibody […] could be such that by controlling the production of specific antibodies it might be possible to find a way of inducing specific gene mutation."[xxi] He ended his letter with a general comment about the immuno-genetic program at CalTech that, which he believed, had "the same general theory as a basis" and recommended to "get a toe hold […] whenever there is an opportunity" since "it cannot be predicted where the break is going to come in attacking a fundamental problem such as

that concerning gene-antigen-antibody interrelations"[xxii] Tyler's research along similar paths concerning the relation between the fertilization processes and the antibody-antigen reaction was recommended by Frank R. Lillie. Lillie wrote that he "felt the subject was very important", when he worked on the topic himself in 1914, but that "it remained neglected for many years until Dr. Tyler has taken it up very seriously and has found in this reaction a subject that lends itself very well to investigation of fundamental problems of immunology."[xxiii]

These and other sources indicate that Sturtevant's, Emerson's and Tyler's research was perceived as a joint and CalTech-specific program towards the application of the antibody-antigen analogy to problems of genetics and embryology. However, the novelty of this approach is not to be found on the purely epistemological level. Analogies between serological, immunological and embryological processes and reactions were quite common in the early 20th century, although neglected thereafter as mentioned in Lillie's recommendation letter. What made research along these lines promising and innovative during the 1940s was the attempt to combine intellectual and material resources and to thereby expose the general importance of the chemical study of specificity.

In 1945, Pauling emphasized in a letter to Hanson concerning a new project application that "the work in immunochemistry and serological genetics" was "very closely connected with the great problem of the structure of proteins in general and I think that the fields of research can contribute significantly to the solution of this great problem."[xxiv] By 1946 Emerson's and Tyler's individual studies on experimental embryology and serological genetics were perfectly integrated in the larger program towards the "Fundamental Problems of Biology and Medicine".[xxv] Tyler and his associates ventured "to assume that all cells are composed of layers of complementary substances that can react with one another in the manner of antigens with their homologous antibodies" and Emerson's work

in serological genetics was from there on said to be "based on the postulate that the specific surface configurations of antigens and enzymes arise from a corresponding specific surface on the gene, and that this surface determines 'gene specificity'". The report ends with the promise that drawing analogies between the enzyme-substrate, resp. antibody-antigen reaction and the newest findings in serological genetics "will open a whole array of genetics and developmental problems to experimental attack from an entirely new direction." [xxvi]

[ii] See e.g. Kay 1993; Hager 1989; Kohler 1991.
[ii] Kay 1993, pp. 149-190.
[iii] Kay 1993, p. 10.
[iv] Kay 1993, p. 136.
[v] Rockefeller Foundation, "The natural and medical sciences cooperative program," 100 Years: The Rockefeller Foundation, accessed March 31, 2014, http://rockefeller100.org/items/show/5666.
[vi] RAC, RF, RG 1.2, series 205, box 4, folder 22.
[vii] RAC, RF, RG 1.1, series 205, box 7, folder 92.
[viii] Mazumdar 1999 illustrates the diversity of specificity concepts and particularly the relation between concepts of species and specificity in her history of immunological thought in the late 19th and 20th century.
[ix] Pauling 1948, pp. 6f.
[x] Bensaude-Vincent and Strengers 1996, p. 157.
[xi] Van't Hoff 1877, pp. 3ff.
[xii] Ramberg 1995, pp. 246ff. and Mazumdar 1999, p. 194.
[xiii] RAC, RF, RG 1.1, series 205, box 7, folder 97.
[xiv] RAC, RF, RG 1.2, series 205, box 4, folder 25.
[xv] RAC, RF, RG 1.2, series 205, box 5, folder 32.
[xvi] RAC, RF, RG 1.2, series 205, box 5, folder 32, pp. 33f.
[xvii] Kay 1993, p. 136.
[xviii] RAC, RF, RG 1.1, series 205, box 7, folder 91.
[xix] RAC, RF, RG 1.1, series 205, Box 7, Folder 93
[xx] RAC, RF, RG 1.1, series 205, box 7, folder 94.
[xxi] RAC, RF, RG 1.1, series 205, box 7, folder 94.
[xxii] RAC, RF, RG 1.1, series 205, box 7, folder 94.
[xxiii] RAC, RF, RG 1.1, series 205, box 7, folder 95.
[xxiv] RAC, RF, RG 1.1, series 205, box 7, folder 96.
[xxv] RAC, RF, RG 1.2, series 205, box 5, folder 32.
[xxvi] RAC, RF, RG 1.2, series 205, box 5, folder 32, p. 35.